Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P 02/101JS/R	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP2003/006092	International filing date (*day/month/year*) 11 June 2003 (11.06.2003)	Priority date (*day/month/year*) 25 June 2002 (25.06.2002)
International Patent Classification (IPC) or national classification and IPC C07K 14/415, C12N 15/11, 15/63, A61K 38/16, 39/36, 48/00		
Applicant MERCK PATENT GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 35 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 14 January 2004 (14.01.2004)	Date of completion of this report 27 September 2004 (27.09.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP2003/006092

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-26, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the claims:

pages _____, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages 1-20, filed with the letter of 10 August 2004 (26.08.2003)

☒ the drawings:

pages 1/5-5/5, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages 1-32, filed with the letter of 26 August 2003 (26.08.2003)

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP2003/006092

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6,8 (both partially)

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 6,8 (both partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The applicant's attention is drawn to the international search report (Box I, point 2, and PCT/ISA 210). The objections raised therein pursuant to PCT Article 5 and PCT Article 6 as concerns claims 6 and 8 are maintained here for the same reasons.

INTERNATIONAL PRELIMINA[redacted] EXAMINATION REPORT

International a[redacted]ication No.
PCT/EP [redacted]06092

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-5, 7, 9-12, 14-20	YES
	Claims	13	NO
Inventive step (IS)	Claims		YES
	Claims	1-5, 7, 9-20	NO
Industrial applicability (IA)	Claims	1-5, 7, 9-20	YES
	Claims		NO

2. Citations and explanations

Reference is made to the following documents:

D1: SUCK R ET AL: "The high molecular mass allergen fraction of timothy grass pollen (Phleum pratense) between 50-60 kDa is comprised of two major allergens: Phl p 4 and Phl p 13" CLINICAL AND EXPERIMENTAL ALLERGY, Vol. 30, No. 10, October 2000 (2000-10), pages 1395-1402, XP002260344 ISSN: 0954-7894

D2: FISHER S ET AL: "Characterization of Phl p4, a major timothy grass (Phleum pratense) pollen allergen" JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, MOSBY - YEARLY BOOK, INC, US, Vol. 98, No. 1, July 1996 (1996-07), pages 189-198, XP000953216 ISSN: 0091-6749

D3: FAHLBUSCH B ET AL: "Detection and quantification of group 4 allergens in grass pollen extracts using monoclonal antibodies" CLINICAL AND EXPERIMENTAL ALLERGY, Vol. 28, No. 7, July 1998 (1998-07), pages 799-807, XP002260345 ISSN: 0954-7894

D4: SUCK R ET AL: "COMPLEMENTARY DNA CLONING AND EXPRESSION OF A NEWLY RECOGNIZED HIGHMOLECULAR MASS ALLERGEN PHL P 13 FROM TIMOTHY GRASS POLLEN (PHLEUM PRATENSE)" CLINICAL AND EXPERIMENTAL ALLERGY,

BLACKWELL SCIENTIFIC PUBLICATIONS, LONDON, GB, Vol. 30, No. 3, March 2000 (2000-03), pages 324-332, XP000953168 ISSN: 0954-7894

D5: STUMVOLL SABINE ET AL: "Purification, structural and immunological characterization of a timothy grass (Phleum pratense) pollen allergen, Phl p 4, with cross-reactive potential." BIOLOGICAL CHEMISTRY, Vol. 383, No. 9, September 2002 (2000-09), pages 1383-1396, XP002260346 ISSN: 1431-6730

The following document is not an international search report citation:

D6: Leduc-Brodard V, Inacio F, Jaquinod M, Forest E, David B, Peltre G: "Characterization of Dac g 4, a major basic allergen from Dactylis glomerata pollen" in J Allergy Clin Immunol. Vol. 98, No. 6 Pt 1, December 1996 (1996-12), pages 1065-1072, XP009032626

1. Novelty

1.1 Claim 13, when it refers to claim 3, covers nothing other than a Phl p 4 polypeptide. However, purified Phl p 4 is already known from **D1** and **D3** (**D1**: figure 1, line 2; D3: figure 1), such that this claim does not meet the requirements of PCT Article 33(2).

Moreover, claim 13 is also not novel when it refers to claim 5, since it then claims a polypeptide which cross-reacts with the allergen Phl p 4. However, D3 discloses that a monoclonal antibody directed against Phl p 4 detects homologous proteins from other grasses, including *Dactylis glomerate* Dac g 4 (D3: figures 6 and 7; page 804, right-hand column, final paragraph, to page 805, left-hand column, line

6). Purified Dac g 4 was already known from D6 (D6: page 1069, right-hand column, final paragraph; page 1070, right-hand column, paragraph 2); thus D6 destroys the novelty of the subject matter of claim 13.

The term "*recombinant*" in relation to the polypeptide in claim 13 changes nothing, since, even if recombinant DNA technology is used, the polypeptide can certainly be identical to the prior art polypeptide. The term "recombinant" indicates only the production method used, but is not automatically associated with technical features that distinguish the polypeptide from the known polypeptide (see PCT Guidelines 5.26-5.27).

1.2 The other claims appear to meet the requirements of PCT Article 33(2).

2. Inventive step

2.1 **D1** can be considered the closest prior art. **D1** discloses the purifying of the principal allergens Phl p 4 and Phl p 13 from *Phleum pratense* (**D1**: page 1396, left-hand column, final paragraph, to right-hand column, paragraph 1; figure 1). The two allergens are presented as important candidates for potential recombinant therapeutic agents for improved immunotherapy (**D1**: abstract).

The present application mentions the polynucleotide and polypeptide sequences of isoforms of the allergen Phl p 4. Recombinant Phl p 4 was expressed in *E. coli* and individual fragments of Phl p 4 with hypoallergenic properties were generated and tested.

In light of the closest prior art, the problem to be solved was that of preparing the complete DNA sequence of Phl p 4 as the basis for therapeutic agents for the improved immunotherapy of grass pollen allergies.

The determining of the coding DNA sequence proceeding from a protein which can repeatedly be obtained in the purified form in the prior art (**D1** and **D3**) *a priori* does not require a person skilled in the art to be inventive today. In the case of group 4 grass pollen allergens from other species, peptide sequences from enzymatic digestion could already be determined (e.g. **D6**: page 1068, right-hand column, paragraph 2). Using the example of the allergen Phl p 13, whose purified form also occurs in the closest prior art, **D1**, **D4** discloses the manner in which a person skilled in the art could proceed when confronted with this problem, namely microsequencing the purified protein or its proteolytic fragments, producing degenerated oligonucleotides on the basis of the partial protein sequences, and amplifying a probe for screening a DNA bank or RACE (**D4**: section entitled "Methods").

As concerns the occurrence of different isoforms of Phl p 4, the applicants themselves state that "the existence of such isoforms is to be expected owing to the heterogenic isoelectric behaviour of natural Phl p 4" and that "all pollen allergens known hitherto comprise such isoforms". Therefore it is not at all unexpected that different isoforms of Phl p 4 exist.

For the above reasons, no inventive step pursuant to PCT Article 33(3) can be recognized in the solution to the problem of determining the primary structure of the group 4 major allergen Phl p 4 from *Phleum pratense*.

3. **Industrial applicability**

Insofar as individual claims have not been excluded from the examination according to Box III, the present claims meet the requirements of PCT Article 33(4).